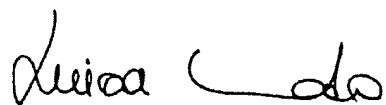


DECLARATION

I, Luisa Currado, hereby sincerely declare that I am conversant with the English and Italian languages and am a competent translator thereof, that to the best of my knowledge and belief the following is a true and correct translation in the English language of the priority document, i.e. Italian patent application for invention n. RM2003A000355196 filed on 18 July 2003.

Signed this 01 day of the month of July 2008



Luisa Currado

MINISTRY OF THE PRODUCTIVE ACTIVITIES
General Directorate of the Productive
Development and Competition
Italian Patent and Trademark Office
Office G2

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Authentication of the copy of the documents relating to the patent application for:
industrial invention

N. RM2003A000355

It is hereby declared that the attached copy is a true copy of the original documents
filed with the above-identified patent application, the data of which are given in the
enclosed official filing certificate.

Rome, March 17, 2004

(seal)

The Officer
Elena Marinelli
(signature)

TO MINISTRY OF COMMERCE AND HANDICRAFT
ITALIAN PATENT AND TRADEMARK OFFICE – ROME (I.P.T.O)

FORM A

DUTY STAMP

PATENT APPLICATION FOR INDUSTRIAL INVENTION, FILING OF SUBSEQUENT DOCUMENTS, PRE-ACCESSIBILITY TO THE PUBLIC

A. APPLICANT(S)

- 1) Name SIGMA-TAU Industrie Farmaceutiche Riunite JN-(Juridical Name) SP (Stock Company)
Residence Rome (RM) code
- 2) Name JN-Juridical Name
Residence code

B. REPRESENTATIVE OF THE APPLICANT BEFORE THE I.P.T.O.

surname name Dott. Marco Sapadaro et al. fiscal code
name of the firm Studio Associato CAVATTONI-RAIMONDI
street Viale dei Parioli n. 160 city Rome Postal Code 00197 (Province) RM

C. ELECTIVE ADDRESS recipient

street n. city Postal Code (Province)

D. TITLE Proposed Class (Section/Class/Subclass) Group/Subgroup

"Combretastatin derivatives with cytotoxic action"

PRE-ACCESSIBILITY TO THE PUBLIC: YES ~~NO~~ IF REQUEST: DATE / / PROTOCOL N°

E. DESIGNATED INVENTORS surname name surname name

- 1) Daniele SIMONI 3) Giuseppe GIANNINI
2) Romeo ROMAGNOLI 4) Domenico ALLOATTI

F. PRIORITY

nation or organization kind of priority application number filing date attached S/R

SUBSEQUENT DOCUMENTS DISSOLUTION

DATE PROTOCOL N°

1) none

2)

G. RECOGNIZED AUTHORITY FOR THE DEPOSIT OF MICRO-ORGANISM CULTURES name

H. SPECIAL REMARKS

duty stamp

ENCLOSED DOCUMENTS

N.items

- Doc. 1) [1] PROV n.pag. 49 abstract with main drawing, description and claims (compulsory 1 item)
Doc. 2) [0] PROV n.sheets drawing (compulsory if cited in the description, 1 item)
Doc. 3) [1] RIS X power of attorney, power or reference to general power
Doc. 4) [0] RIS designation of the inventor
Doc. 5) [0] RIS priority documents with Italian translation
Doc. 6) [0] RIS authorization or assignment deed
Doc. 7) [0] full name of the applicant

8) Certificates of payment, total euro Onehundredeightyeight/51

COMPILED THE 18/07/2003

Signature of Applicant(s)

Dott. Marco SPADARO

CONTINUES YES/NO YES

A CERTIFIED COPY OF THE PRESENT DOCUMENT IS REQUIRED YES/NO YES

CHAMBER OF COMMERCE INDUSTRY HANDICRAFT AND AGRICULTURE - ROME CODE 58

FILING RECEIPT APPLICATION NUMBER RM2003A000355

Year two thousand three day eighteen month of July

The above applicant(s) has/have submitted to the undersigned this application accompanied by No. [00] additional sheets for the granting of the above patent.

I. Various Remarks by the Recording Officer:

Filing Person

(stamp)

The Recording Officer

(signature illegible)

(signature illegible)

ADDITIONAL SHEET A

Additional sheet of total application N. REGA

RM2003A000355

A. APPLICANT(S)

Name	JN-Juridical Name
Residence	code
Name	JN-Juridical Name
Residence	code
Name	JN-Juridical Name
Residence	code
Name	JN-Juridical Name
Residence	code
Name	JN-Juridical Name
Residence	code

E. DESIGNATED INVENTORS

surname name

surname name

Claudio PISANO

F. PRIORITY

nation or organization kind of priority application number filing date attached S/R

SUBSEQUENT DOCUMENTS DISSOLUTION

DATE

PROTOCOL N°

Signature of Applicant(s)

Dott. Marco SPADARO

 Space for the Italian Patent and Trademark Office

SEAL

ABSTRACT OF THE INVENTION WITH MAIN DRAWING, DESCRIPTION AND
CLAIMS FORM A

APPLICATION No RM2003A00355

REG A

FILING DATE 18/07/2003

PATENT No.

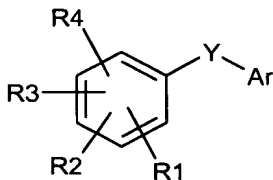
GRANT DATE

D. TITLE

"Combretastatin derivatives with cytotoxic action"

L. ABSTRACT

The present invention described relates to new combretastatin derivatives obtained by total synthesis and having the following general formula:



in which the groups are as defined in the description here below.

Said compounds, though chemically related to the structure of cis/trans-combretastatin, do not always bind tubulin, but nevertheless exhibit cytotoxic activity of interest in the oncological field as anticancer and/or antiangiogenic agents.

M. DRAWING

DULY STAMP AND SEAL

Description of the invention entitled:

"Combretastatin derivatives with cytotoxic action"

filed in the name of: SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.

nationality Italian

with registered office in: Viale Shakespeare, 47 - 00144 Roma RM

Inventors: Daniele SIMONI

Romeo ROMAGNOLI

Giuseppe GIANNINI

Domenico ALLOATTI

Claudio PISANO

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The present invention relates to new combretastatin derivatives obtained by total synthesis, to procedures for their preparation, to their use as medicines and to compositions containing them. The development strategy for each product has been selected from the group consisting of: (i) substitution of the olefinic bond with a heterocycle of the isoxazole or 4,5-dihydro-3-R-isoxazole type, or ii) substitution of one or both H's present on the olefinic bond with a fluorine and/or iii) substitution of an aromatic residue with an aromatic heterocyclic residue of the benzofuran, benzothiophene, indole and indazole, furan or thiophene type, or with naphthyl groups, with possibly functionalised substituent groups, and/or iv) substitution of one or more methoxyl residues on the trimethoxyphenyl with other substituents. Said compounds, though chemically related to the structure of cis/trans-combretastatin, do not always bind tubulin, but nevertheless exhibit a cytotoxic activity of interest in the oncological field as anticancer or antiangiogenic agents.

Antitubulin activity is not regarded as an essential requisite for anticancer activity; in actual fact, the anticancer activity of combretastatin is the result of a series of pharmacodynamic- and pharmacokinetic-type components.

Background to the invention

Angiogenesis in the adult is normally quiescent, yet it constitutes a normal function, for example in the healing of wounds or in the reconstruction of the endometrium during the female reproductive cycle. The angiogenic response is physiologically stimulated when the vascular functions are reduced and tissue perfusion inadequate.

More generally, it can be claimed that angiogenesis, in physiological conditions, constitutes a form of positive feedback in response to inadequate perfusion, or to a reduced supply of oxygen and nutrients, as, for instance, in the case of occlusion of an artery, in situations of growth of tissue mass (e.g. the neovascularisation that accompanies the formation of muscle tissue); and in the case of an increased work load associated with an increased oxygen and nutrient requirement. In the course of local ischaemia, due to partial or complete occlusion of an artery, the development of collateral vessels is necessary in order to maintain perfusion.

The growth of a primary tumour is known to be favoured by good vascularisation of the tumour tissue. An adequate supply of oxygen and nutrients favours the rapid growth of the tumour itself. It has been demonstrated that the extent of neoangiogenesis is a highly adverse factor in the prognosis of neoplasms (*van Hinsbergh, V.W., Collen, A., Koolwijk, P.: Ann. On-col., 10 Suppl., 4:60-3, 1999; Buolamwini, J.K.: Curr., Opin., Chem.,*

Biol., 3(4):500-9, 1999).

Research directed towards the discovery of new-generation chemotherapeutic agents has identified tubulin as a possible cell target. Substances capable of altering microtubule aggregation are also capable of inhibiting cell proliferation.

The microtubules play a very important role in the regulation of the cell architecture, in cell division and in cell metabolism. The systems of the microtubules of eukaryotic cells include the dynamic organisation of the aggregation and disaggregation of the matrix in which tubulin heterodimers polymerise to form microtubules both in cancer cells and in normal cells. Cytotoxic agents capable of altering the polymerisation or depolymerisation of the microtubules prove to be effective chemotherapeutic agents.

Combretastatin A-4 (CA-4), isolated from a variety of African willow, *Combretum caffrum* (Combretaceae) (Pettit, G.R. et al.: *Experientia*, 1989, 45, 209), exhibits promising anticancer potential with an antitubulin mechanism, strongly binding tubulin in a site very similar to that to which colchicine binds (Lin, C.N. et al.; *Biochemistry*, 1989, 28, 6984). Said binding to tubulin prevents its polymerisation to microtubules with an antimitotic effect. CA-4 inhibits cell growth even at very low concentrations, of the order of nanomoles.

The phosphate salt of CA-4 - "CA-4P" (Pettit, G.R. et al.; *Anti-cancer Drug Des.* 1995, 10, 299), - is hydrosoluble and is currently inserted in phase II clinical trials.

The ability of combretastatin to selectively impair tumour neovascularisation makes this compound distinctly interesting and prompts the search for new and more potent compounds.

Recently, many studies have demonstrated that a substantial number of compounds with antiangiogenic activity, such as CA-4P, are capable of inhibiting the neovascularisation of the retina in well characterised murine models of forms of retinopathy. These studies suggest that both CA-4P and the new derivatives could be usefully employed as antiangiogenic agents in the fields of both oncology and ophthalmology (*Griggs J. et al.: Am. J. Pathol. 2002, 160(3), 1097-103*).

Nevertheless, the very substantial cytotoxic potency of combretastatin cannot be put down only to its antitubulin effect. There are compounds of analogous structure which, though exhibiting substantial cytotoxicity, do not exert an equally high degree of antitubulin activity.

In addition to the pharmacokinetic aspects, there are many pharmacodynamic aspects which are still the subject of thorough investigation, and, as things stand at present, there are not enough literature data available to furnish a definitive response (*Le Wang et al.: J. Med. Chem, 2002, 45, 1697-1711*).

From the chemical standpoint it is known that the distance between the two aromatic rings of combretastatin, colchicine or their derivatives constitutes an immutable requirement of this class of compounds for their antitubulin properties (*McGown, A.T. et al.; a) Bioorg. Med. Chem. Lett., 1988, 8(9), 1051-6; b) Bioorg. Med. Chem. Lett. 2001, 11(1), 51-4*).

Substitution of the double bond with an indolyloxazoline residue (*Qun Li, Q. et al.: Bioorg. Med. Chem. Lett., 2002, 12(3), 465-9*) has led to a combretastatin derivative, A-289099, (where an aromatic ring is also

substituted with an N-Me-indole residue), with anticancer activity comparable to that of the comparator reference product.

It is equally well known in the cancer field that a fundamental stage in the biology of tumour cells consists in their acquiring the ability to cause metastases.

Tumour cells that metastasise have the ability to lose adhesion to the surrounding structures, invade blood and lymph vessels and colonise other tissues at a distance where they then continue to reproduce.

Metastatic spread is also a critical event in the clinical history of the disease, being the main cause of death from cancer. It is closely associated with, and favoured by the presence of vascular tissue in the tumour site or in the adjacent areas.

In fact, cancer cell migration through the surrounding structures allows the cells to reach the blood vessels in the tumour, whether pre-existing or formed by neoangiogenesis, and from where they then proceed to the bloodstream (Ray, J.M., Stetler-Stevenson, W.G.: *Eur. Respir. J.*, 1994, 7(11):2062-72; Stetler-Stevenson, W.G., Liotta, L.A., Kleiner D.E. Jr.: *FASEB J.*, 1993, 7(15):1434-41).

The presence of communication paths between lymphatic and blood vessels allows cancer cells to move in both vascular systems.

Recent studies have revealed a direct relationship between angiogenesis and arthritic disease (Koch, A.E.: *Arthritis and Rheumatism*, 1998, 41:951-962). In particular, it has been demonstrated that neovascularisation of the articular cartilages plays a crucial role in the formation of the pannus and in the progression of arthritis. A normal cartilage has no blood vessels,

whereas the sinovial fluid of arthritic patients contains an angiogenesis-stimulating factor produced by the endothelial cells (endothelial-cell-stimulating angiogenesis factor = ESAF).

The presence of this factor is associated with the vascularisation and degradation of the cartilage.

Other diseases are also related to abnormal angiogenesis.

It has been found that neovascularisation of the affected tissues is a causative factor favouring diabetic retinopathy (*Histol. Histopathol.*, 1999; 14(4):1287-94), psoriasis (*Br. J. Dermatol.*, 1999 141(6):1054-60), chronic inflammation and atherosclerosis (*Planta Med.*, 1998; 64(8):686-95).

Control of neovascularisation is therefore one of the fundamental elements for the control and treatment of such diseases.

Despite the progress made over the past few years in the sector of new drugs endowed with antiangiogenic activity, this sector of research is regarded by many experts in the field of medicine as still being one of the most promising for the discovery of new drugs for the treatment of diseases characterised by abnormal angiogenesis, particularly tumours.

In fact, for these diseases it is still strongly perceived the need for new compounds presenting fewer side effects and which are capable of blocking or interfering with the abnormal mechanisms underlying the above-mentioned diseases and which therefore allow such diseases to be treated.

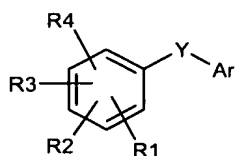
It has now surprisingly been found that by modifying both the double olefinic bond and the aromatic rings of combretastain, the result is the general formula (I) compounds described here below, with antitubulin and/or cytotoxic

properties, which are useful agents for the treatment of diseases caused by abnormal angiogenesis and of tumours.

In a thoroughly unexpected manner, the derivatives according to the present invention show that the cytotoxic activity can still be very substantial even in the presence of low or non-existent antitubulin activity.

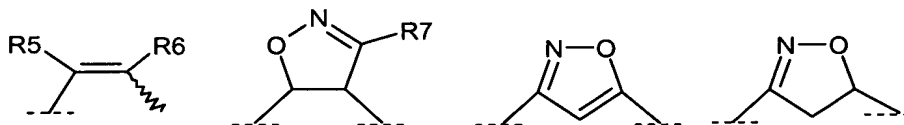
Summary of the invention

One subject of the present invention are formula (I) compounds



in which

the various R_1 , R_2 , R_3 and R_4 , which can be the same or different, are H, OH, OPO_3Na_2 , OMe, NO_2 , F, Cl; Br



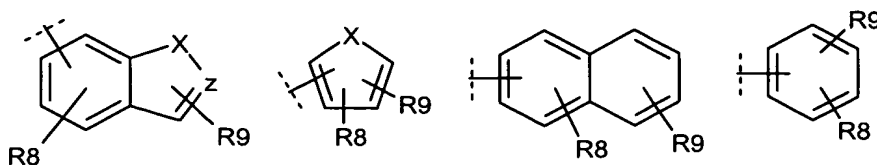
wavy : *cis* or *trans*

Y is a group selected from

R_5 and R_6 , which can be the same or different, are H, or halogen, but cannot both be simultaneously H;

R_7 is H, OMe, SO_2Ph ;

Ar is a group selected from:



R_8 and R_9 , which can be the same or different, are H, OH, OMe, OPO_3Na_2 , NH_2 , NHR_{10} , NO_2 , or halogen;

R_{10} is C_1 - C_4 alkyl or acyl;

X is O, S, N, NR_{11} ;

R_{11} is H, CH_3 , CH_2Ph ;

Z is CH, N;

their enantiomers, diastereoisomers, the respective mixtures and their pharmaceutically acceptable salts.

The invention relates to formula (I) compounds and to their use in the medical field.

A further subject of the present invention are pharmaceutical compositions containing as their active ingredient a formula (I) compound and at least one pharmaceutically acceptable excipient or diluent.

A further subject of the present invention is the use of a formula (I) compound for the preparation of a medicine possessing cytotoxic-type anticancer activity.

A further subject of the present invention is the use of a formula (I) compound for the preparation of a medicine with antiangiogenic-type anticancer activity.

A further subject of the present invention is the use of a formula (I) compound for the preparation of a medicine useful for the prevention and reduction of cancer metastases.

A further subject of the present invention is the use of formula (I) compounds for the preparation of a medicine with anticancer activity, in which the cancer is selected from the group consisting of: sarcoma, carcinoma, carcinoid, bone cancer, endocrine cancer, lymphoid leukaemia, myeloid leukaemia, monocytic leukaemia, megakaryocytic leukaemia, or Hodgkin's disease.

A further subject of the present invention is the use of a formula (I) compound for the preparation of a medicine for the treatment of diseases related to abnormal angiogenesis in which the disease is selected from the group consisting of arthritic disease, tumours, metastatic spread, diabetic retinopathy, psoriasis, chronic inflammation, and atherosclerosis.

Detailed description of the invention

According to the present invention, pharmaceutically acceptable salts are all those salts that the expert in the sector is capable of preparing, without the acid or base utilised giving rise to unwanted effects, when said salts are used as medicines.

Particularly preferred compounds are:

2-methoxy-5-[3-methoxy-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-phenol - ST1996;

2-methoxy-5-[3-methoxy-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol - ST1998;

5-[3-benzenesulphonyl-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-2-methoxy-phenol - ST1995;

5-[3-benzenesulphonyl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-2-methoxy-phenol - ST1997;

2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol - ST1999;

2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-3-isoxazolyl]-phenol - ST2001;

2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-3-isoxazole]-phenol - ST2002;

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-4-ol - ST2151;

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thio-phen-4-ol - ST2152;

cis-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene - ST2049;

trans-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene - ST2050;

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol - ST2179;

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol - ST2180;

cis-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran - ST2051;

trans-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofura-n - ST2052;

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-7-ol - ST2487;

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thio-phen-7-ol -
ST2488;

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol - ST2491;

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol - ST2492;

cis-1-methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphtha-lene -
ST2053;

methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalene - ST2054;

cis-7-methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-
indazole - ST2055;

trans-7-methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-
indazole - ST2056;

2-nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-thiophene - ST2057;

2-nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-furan - ST2058;

cis-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol - ST2181;

trans-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol - ST2182;

disodium 6[(Z)-2-(3,4,5-trimethoxy-phenyl)ethenyl]-1-benzo-thiophen-4-
ol 4-O-phosphate - ST2495;

disodium 6[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1-benzo-furan-4-ol 4-
O-phosphate, - ST2496.

The compounds described in this invention were prepared according to synthesis diagrams 1-7.

In particular, the formula (I) compounds in which Y is the isoxazoline ring and R₇ is a phenylsulphonic residue, such as, for example, the compounds called ST1995 and ST1997, were prepared according to diagram 1 through the dipolar cycloaddition reaction [3+2]-of the nitryloxide generated by

nitroderivative **2** on suitably protected combretastatin. Removal of the protective group, such as *tert*-butyl-dimethylsilyl, leads to the desired compounds ST1995 and ST1997.

On the other hand, in those cases in which the R_7 group is methoxy, as, for example, in the compounds called ST1996 and ST1998, the compounds are obtained through the substitution of the phenylsulphonic group, as in the previous compounds ST1995 and ST1997, by means of reaction with sodium methoxylate.

The regioisomeric isoxazoline derivatives, such as, for example, ST1999 and ST2001, were prepared according to synthesis diagrams 2 and 3 through the dipolar cycloaddition reactions [3+2]-between nitryloxides generated by oximes **5** and **10** and the alkene components **6** and **9**, respectively. Removal of the *tert*-butyl-dimethylsilyl protective group leads to the desired products.

The regioisomeric isoxazole derivatives, such as, for example ST2000 and ST 2002, were in turn prepared through the manganese-dioxide-mediated oxidation of the isoxazolines described above, suitably protected according to synthesis diagrams 2 and 3. Removal of the protective group, such as *tert*-butyl-dimethylsilyl, leads to the desired products.

The formula (I) compounds in which Ar is a benzothiophene or benzofuran residue, such as, for example, compounds ST2151, ST2152, ST2049, ST2050, ST2179, ST2180, ST2051, ST2052, ST2487, ST2488, ST2491 and ST2492, were obtained according to the synthesis procedures described in synthesis diagrams 4 and 5.

In particular, the Wittig reaction between aldehydes **17a-d** and phosphonium salt **18**, followed by removal of the *tert*-butyl-dimethylsilyl

protective group, made it possible to obtain the desired derivatives (diagram 4). In the same way, the Wittig reaction between aldehydes **26a,b** and phosphonium salt **18**, followed by removal of the appropriate protective group, such as *tert*-butyl-dimethylsilyl, made it possible to obtain the desired derivatives, for example, ST2487, ST2488, ST2491 and ST2492 (diagram 5).

A similar procedure was used to prepare the derivatives in which Ar is a naphthalene, indazole, nitrothiophene or nitrofuran residue, such as, for example, ST2053, ST2054, ST2055, ST2056, ST 2181, ST2057, ST2058, and ST2182 (diagram 6) through the Wittig reaction between the appropriate aldehydes **29a-d** and phosphonium salt **18**.

Lastly, the formula (I) compounds in which R₈ or R₉ are a phosphate group, such as, for example, ST2495 and ST2496, were obtained according to the synthesis procedure described in diagram 7 starting from the corresponding phenol derivatives, such as, for example, ST2151 and ST2179.

In the medical field the use is known of therapeutic protocols involving the administration of more than one anticancer drug simultaneously or in sequence, for example, as a function of the synchronisation of the cell cycles, with which experts in oncology are thoroughly familiar.

The need to administer more than one anticancer drug in therapeutic protocols is due to the fact that the drugs, by acting at different metabolic levels, favour, in some cases, complete remission of the cancer, and in other cases lengthen the life and/or improve the quality of life of the patient treated. The combination according to the present invention lends itself to use concomitantly with one or more known anticancer drugs for the treatment of tumours,.

A further subject of the present invention is therefore the use of formula (I) compounds, whether alone or in combination with other known antiproliferative drugs, selected from the group consisting of: alkylating agents; topoisomerase inhibitors; antitubulin agents; intercalating agents; antimetabolites; naturally occurring products such as Vinca alkaloids, epipodophyllotoxins, antibiotics, enzymes, taxanes and anticancer vaccines.

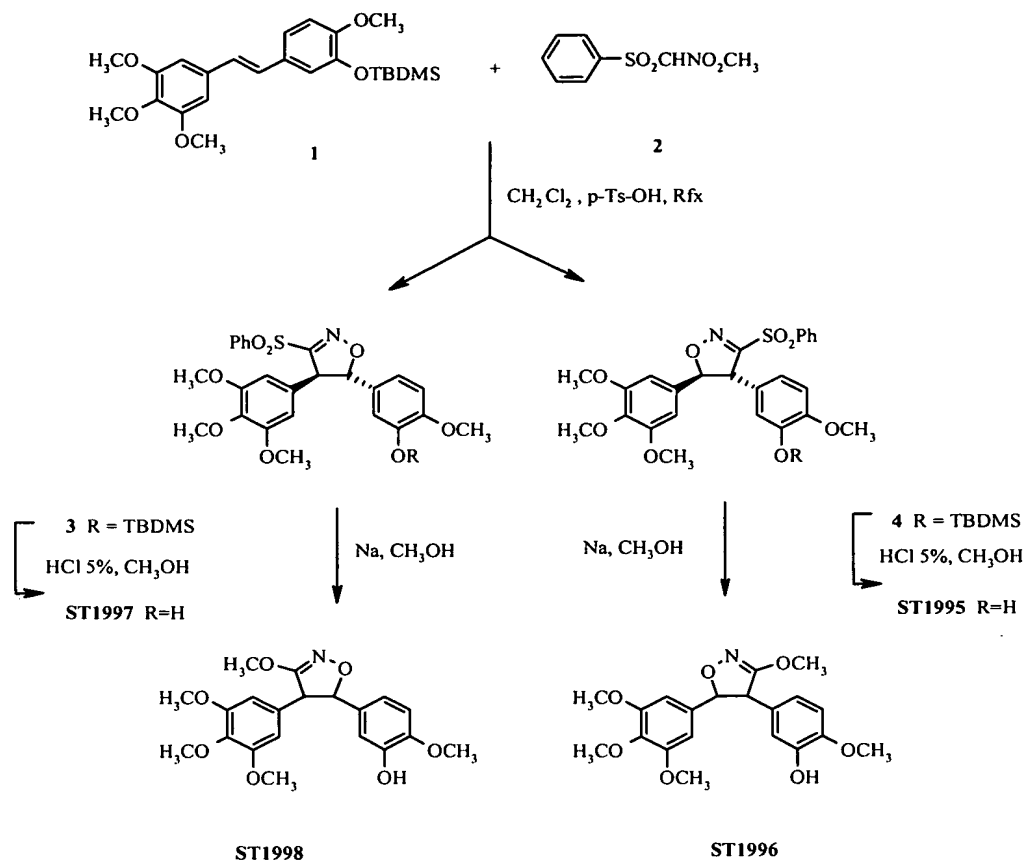
The following examples illustrate the invention.

Example 1

Preparation of ST1995, ST1996, ST1997 and ST1998

These compounds are prepared according to synthesis diagram 1 here below:

SCHEMA 1

Preparation of isoxazolines 3 and 4

To the flask containing nitronic ester **2** prepared according to the procedure described by Wade *et al.* (*J. Org. Chem.* 1981, 46, 765-770) is added alkene **1** (600 mg, 1.4 mmol) dissolved in CH_2Cl_2 (6 ml) and $p\text{-toluenesulphonic acid monohydrate}$ (270 mg, 1.4 mmol). The reaction is refluxed for 30 minutes in an argon atmosphere. After bringing the solution back to room temperature CH_2Cl_2 (15 ml) is added, and washings are performed with 5% NaOH (10 ml), H_2O (10 ml) and brine (10 ml). The organic phase, anhydriified on Na_2SO_4 , is evaporated at reduced pressure. Chromatographic purification of the crude product made it possible to obtain products **3** and **4** with an overall yield of 20%.

Preparation of ST1996 and ST1998

Metallic Na (130 mg, 0.6 mmol) is dissolved in MeOH (10 ml), the solution thus obtained is added to the appropriate phenyl-sulphonyl derivative 3, 4 (0.15 mmol) and the reaction is left at room temperature for 6 h.

After concentrating the ethanol and diluting with CH_2Cl_2 (15 ml), extractions are performed with H_2O (8 ml) and brine (8 ml). The organic solution, anhydried on Na_2SO_4 , is evaporated at reduced pressure. The crude product obtained is purified by chromatography.

2-Methoxy-5-[3-methoxy-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-phenol – ST1996

Yield: 70%, m.p. = 160-162 °C; ^1H NMR (CDCl_3) δ 3.84 (s, 9H), 3.91 (s, 6H), 4.19 (d, 1H, $J = 9.2$ Hz), 5.38 (d, 1H, $J = 9.3$ Hz), 5.69 (s, 1H), 6.54 (s, 2H), 6.69-6.74 (m, 1H), 6.84-6.88 (m, 2H).

2-Methoxy-5-[3-methoxy-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol – ST1998

Yield: 65%. Oil. ^1H NMR (CDCl_3) δ 3.86 (s, 9H), 3.91 (s, 6H), 4.14 (d, 1H, $J = 9.1$ Hz), 5.40 (d, 1H, $J = 9.1$ Hz), 5.68 (br, 1H), 6.43 (s, 2H), 6.84 (s, 2H), 6.95 (s, 1H).

Preparation of ST1995, ST1997

The appropriate silyl derivative (0.1 mmol) 3,4 is dissolved in MeOH (10 ml), and H_2O (1/2 ml) and HCl 5% (10 drops) are added to the solution. After being left overnight at room temperature, the methanol is evaporated, the crude product is extracted with CH_2Cl_2 (15 ml), and washed with H_2O (10 ml) and brine (10 ml). The organic solution, anhydried and evaporated to

dryness, produces a crude product that is purified by chromatography on silica gel.

5-[3-Benzenesulphonyl-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-2-methoxy-phenol – ST1995

Yield: 95%. Oil. ^1H NMR (CDCl_3) δ 3.67 (s, 6H), 3.82 (s, 3H), 3.91 (s, 3H), 4.58 (d, 1H, $J = 6.5$ Hz), 5.56 (d, 1H, $J = 6.5$ Hz), 5.62 (br, 1H), 6.15 (s, 2H), 6.79-6.84 (m, 3H), 7.37-7.43 (m, 2H), 7.55 (d, 1H, $J = 8.1$ Hz), 7.61-7.65 (m, 2H).

5-[3-Benzenesulphonyl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-2-methoxy-phenol – ST1997

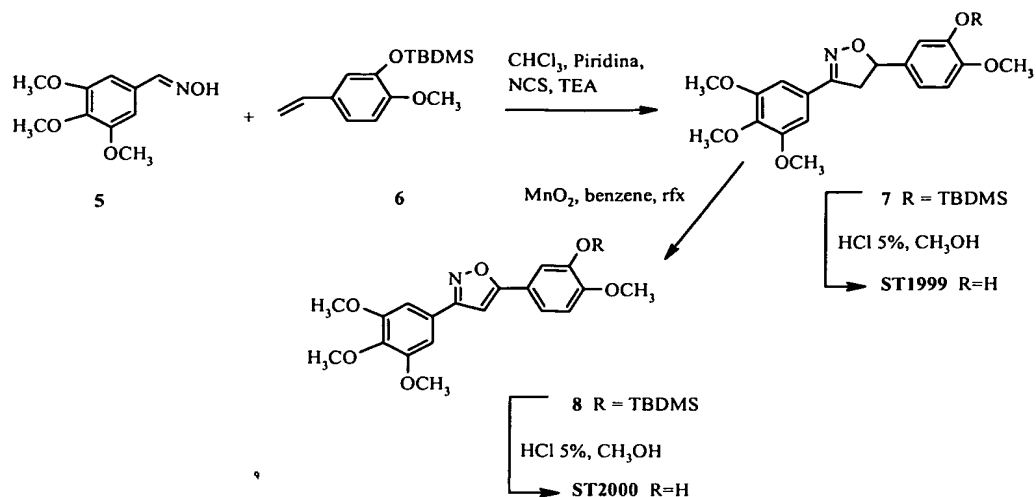
Yield: 85%. Oil. ^1H NMR (CDCl_3) δ 3.82 (s, 6H), 3.84 (s, 3H), 3.89 (s, 3H),), 4.56 (d, 1H, $J = 6.6$ Hz), 5.55 (d, 1H, $J = 6.5$ Hz), 5.57 (br, 1H), 6.39 (s, 2H), 6.56-6.58 (m, 1H), 6.62 (d, 1H, $J = 2.1$ Hz), 6.71 (d, 1H, $J = 8.1$ Hz), 7.37-7.44 (m, 2H), 7.55-7.59 (m, 1H), 7.66-7.72 (m, 2H).

Example 2

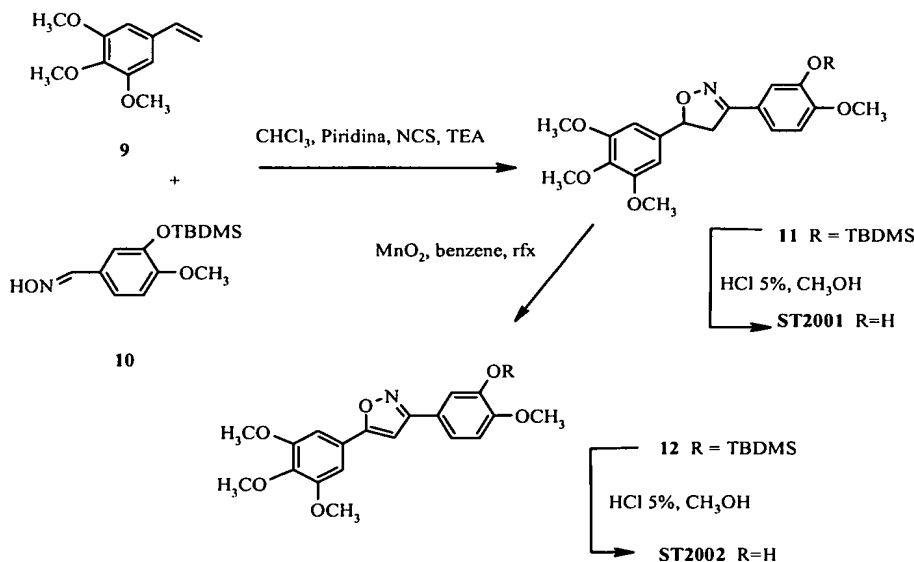
Preparation of ST1999, ST2000, ST2001 and ST2002

These compounds are prepared according to synthesis diagrams 2 and 3 here below:

SCHEMA 2



SCHEMA 3

General procedure for preparation of 7 and 11.

To a flask containing anhydrous CH_2Cl_2 (7 ml) are added NCS (1 mmol, 133 mg), pyridine (0.1 mmol, 7.9 mg, 8 μl) and the appropriate oxime 5, 10 (1 mmol). The reaction is stirred at 50°C for 1 h. The corresponding alkene 6, 9 (1.1 mmol) is then added at room temperature and TEA (1.5 mmol, 152 mg, 0.2 ml) is added dropwise very slowly. The reaction mixture is left to stir for 2 h. CH_2Cl_2 (20 ml) is then added, and washings are performed with H_2O (15 ml),

2.5% HCl (10 ml), H₂O (10 ml) and brine (10 ml). The organic phase is anhydriified on Na₂SO₄ and concentrated at reduced pressure. The crude reaction product is purified by chromatography to give the desired isoxazoline. Yield of the cycloaddition: 70-75%.

General procedure for the preparation of isoxazoles 8 and 12

Isoxazoline 7, 11 (50 mg, 0.1 mmol) is dissolved in benzene (15 ml), MnO₂ (450 mg, 5.17 mmol) is added to the solution, and the mixture is refluxed with Dean-Stark for 6 h under vigorous stirring.

The reaction mixture, brought back to room temperature, is filtered on celite and the filtrate is concentrated at reduced pressure.

The crude product thus obtained is purified by chromatography to give the isoxazole derivative. Oxidation yield: 80-85%.

The final compounds ST1999, ST2000, ST2001 and ST2002 are obtained from the corresponding precursors 7, 8, 11 and 12 through desilylation performed as described above for ST1997 and ST1995.

2-Methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol – ST1999

Yield: 85%, Oil, ¹H-NMR (CDCl₃) δ: 3.30 (dd, 1H, J = 8.2 Hz, 16.2 Hz), 3.74 (dd, 1H, J = 10.9 Hz, 16.3 Hz), 3.89 (s, 12H), 5.65 (dd, 1H, J = 8.2 Hz, 10.8 Hz), 5.63 (br, 1H), 6.85-6.95 (m, 5H).

2-Methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-5-isoxazolyl]-phenol – ST2000

Yield: 95%, m.p.: 183-185°C, ¹H-NMR (CDCl₃) δ: 3.91 (s, 3H), 3.95 (s, 3H), 3.96 (s, 9H), 5.80 (br, 1H), 5.82 (s, 1H), 6.94 (d, 1H, J = 8.9 Hz), 7.08 (s, 2H), 7.37- 7.41 (m, 2H).

2-Methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-3-isoxazolyl]-phenol – ST2001

Yield: 90%, m.p.: 128-130 °C, ¹H-NMR (CDCl₃) δ: 3.30 (dd, 1H, J = 8.4 Hz, 16.2 Hz), 3.75 (dd, 1H, J = 10.4 Hz, 16.4 Hz), 3.86 (s, 3H), 3.90 (s, 6H), 3.96 (s, 3H), 5.65 (dd, 1H, J = 8.2 Hz, 10.2 Hz), 5.68 (br, 1H), 6.62 (s, 2H), 6.90 (d, 1H, J = 8.1 Hz), 7.22 (dd, 1H, J = 2.1 Hz, 8.2 Hz), 7.28 (d, 1H, J = 2.1 Hz).

2-Methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-3-isoxazole]-phenol – ST2002

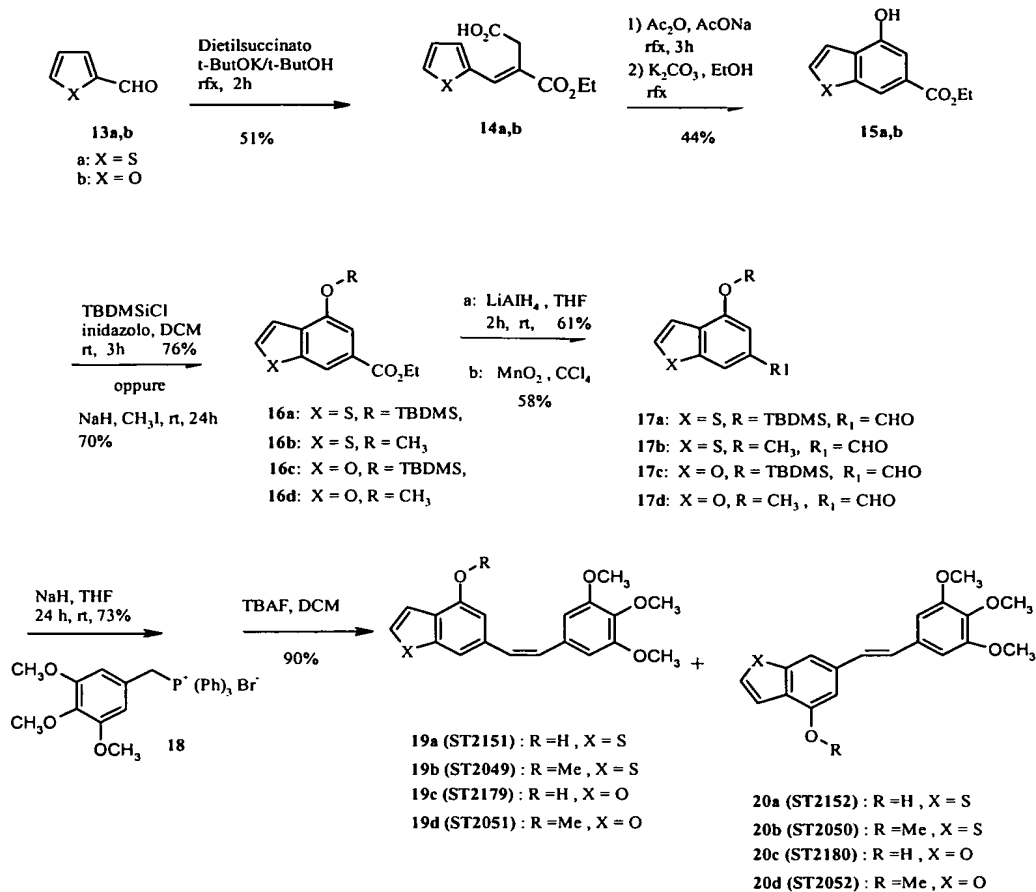
Yield: 80%, m.p.: 205-206 °C, ¹H-NMR (CDCl₃) δ: 3.90 (s, 3H), 3.95 (s, 9H), 5.80 (br, 1H), 6.70 (s, 1H), 6.93 (d, 1H, J = 8.3 Hz), 7.04 (s, 2H), 7.36 (d, 1H, J = 2 Hz), 7.43 (dd, 1H, J = 1.9 Hz, 8.2 Hz).

Example 3

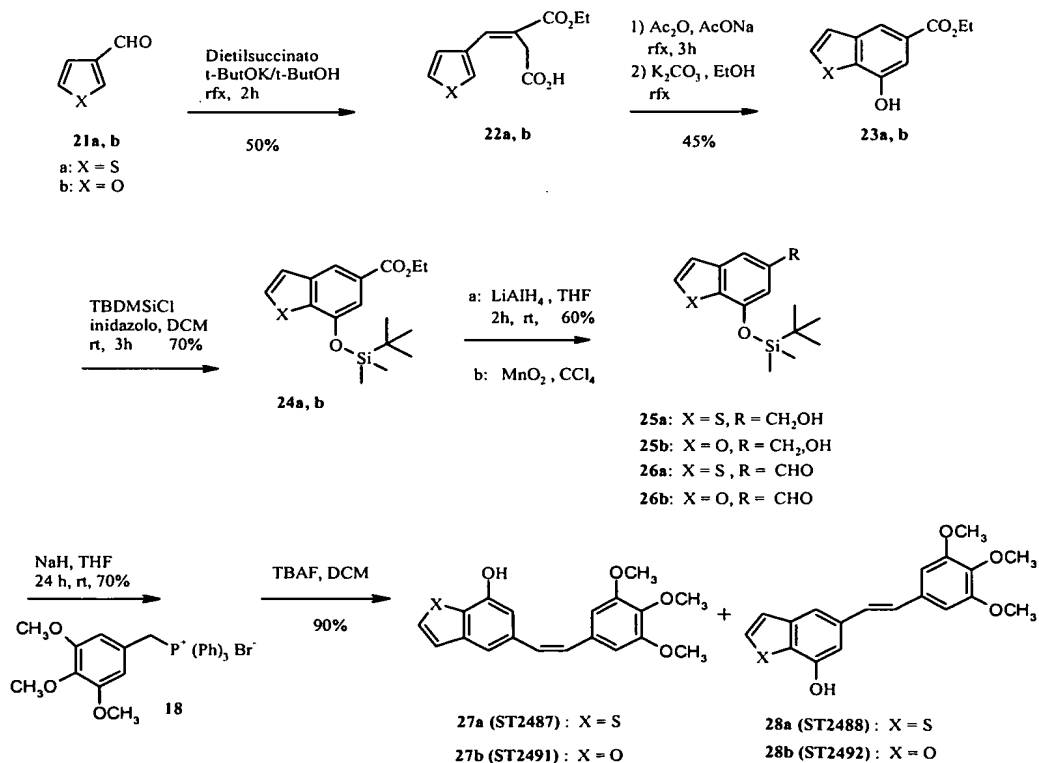
Preparation of ST2151, ST2152, ST2179, ST2180, ST2049, ST2050, ST2051, ST2052, ST2487, ST2488, ST2491 and ST2492.

These compounds are prepared according to synthesis diagrams 4 and 5 here below:

SCHEMA 4



SCHEMA 5



General procedure for obtaining 15a,b and 23a,b

To a suspension of t-BuOK (17 g.; 150 mmol, 3 equiv.) in t-BuOH (50 mL) is added a mixture of aldehyde 13a-b, 21a-b (50 mmol) in diethylsuccinate (32 mL, 225 mmol, 4.5 mmol). The reaction is refluxed for 45 minutes. After this time period the same amounts of t-BuOK, t-BuOH and diethylsuccinate are added and the mixture is left at reflux for another 45 minutes. It is then brought to room temperature, and acidified (pH 2) with an aqueous solution of HCl (20% v/v). The mixture is diluted with 5% HCl (100 mL) and extracted with EtOAc (3x100 mL). The organic phase is then extracted with 10% aqueous solution in Na₂CO₃ (4 x 50 mL); the pooled aqueous phases are washed with Et₂O (50 mL) and then acidified to pH = 2 with HCl (20% v/v). The aqueous phase is finally extracted with EtOAc (4 x 50 mL) and the anhydriified pooled organic extracts are concentrated at reduced pressure, giving acid ester 14a-b, 22a-b with a quantitative yield. The crude product (14a-b, 22a-b) obtained with the previous reaction (50 mmol) is solubilised in a mixture consisting of acetic anhydride (100 mL) and anhydrous CH₃CO₂ Na (200 mmol, 4 equiv.). The solution thus obtained is brought to the boil for 5 hours, after which it is evaporated to dryness. The residue is extracted with an aqueous solution (75 mL) of Na₂CO₃ (15%) and extracted with EtOAc (3 x 50 mL). The pooled organic extracts are washed with brine (50 mL), anhydriified (Na₂SO₄) and purified by flash chromatography on silica gel.

A suspension of acetyl derivative (10 mmol) and anhydrous K₂CO₃ (1.4 g., 10 mmol) in EtOH (20 mL) is refluxed for 18 hours, after which it is filtered and the filtrate evaporated to dryness. The residue is solubilised in water (20

mL), the aqueous phase is acidified (pH = 2) with HCl (10% v/v) and then extracted with EtOAc (3 x 20 mL). The pooled organic extracts are anhydriified (Na_2SO_4), concentrated at reduced pressure and purified by flash chromatography on silica gel.

15a: brown solid, m.p. = 134-136°C; 15b: white solid, m.p. = 105-107°C;
23a: brown solid, m.p. = 145-147°C; 23b: white solid, m.p. = 165-167°C.

Preparation of 16b, 16d

To a suspension consisting of compound 15a,b (5 mmol) and anhydrous K_2CO_3 (5 mmol, 690 mg, 1 equiv.) in THF (20 mL) is added Me_2SO_4 (5 mmol, 630 mg, 0.48 mL) and the resulting solution is brought to the boil for 8 h. After this period the mixture is filtered, evaporated to dryness and the residue extracted with a mixture of EtOAc (20 mL) and water (5 mL). The organic phase is washed with brine (5 mL), anhydriified and concentrated in vacuo. The resulting residue is purified by flash chromatography on silica gel. Derivatives 16b,d are obtained as colourless oils.

Preparation of 16a,c and 24a,b

To a solution of phenol 15a-b, 23a-b (3 mmol) in DCM (10 mL) are added TBDMSCl (3.6 mmol, 1.2 equiv., 550 mg) and imidazole (7.5 mmol, 2.5 equiv., 510 mg). The mixture is left at room temperature for 18 hours, after which it is diluted with DCM (10 mL), washed with water (5mL) and brine (5 mL) and the organic phase is anhydriified. After concentration, the residue is purified by flash chromatography on silica gel. Derivatives 16a, 16c, 24a and 24b are obtained as colourless oils.

Preparation of 17a-d and 26a,b

The appropriate ester 16a-d, 24a,b (2 mmol) dissolved in THF (5 mL) is added dropwise at 0°C to a suspension of LiAlH_4 (3 mmol, 114 mg, 1.5 equiv.) in 10 mL of THF. On completion of the addition, the reaction is left for a further 30 minutes at 0°C and then for 2 h at room temperature. The reaction is then cooled again with a water and ice bath, the excess LiAlH_4 is decomposed with an aqueous soda solution (5%); the reaction mixture is filtered on celite, and the filtrate extracted with EtOAc (15 mL) and water (5 mL). The organic phase is then washed with brine (5 mL), anhydriified (Na_2SO_4) and evaporated to dryness. The product obtained is purified by flash chromatography on silica gel. To a solution of the alcohol derivative obtained by chromatography (1 mmol) in CCl_4 (25 mL) is added MnO_2 (1.1 mmol, 1.1 equiv.). After 2 h at room temperature, the mixture is filtered and the filtrate evaporated to dryness and used for the next reaction without any further purification.

Preparation of ST2151, ST2152, ST2179, ST2180, ST2049, ST2050, ST2051 and ST2052

To a solution of aldehyde 17a-d, 26a,b (2 mmol) in 10 mL of anhydrous THF is added phosphonium salt 18 (2 mmol, 1.05 g., 2 equiv.). The suspension thus obtained is cooled with a water and ice bath, and NaH (50% in mineral suspension, 2.2 mmol, 1.1 equiv., 110 mg) is then added. It is left to stir at room temperature for 24 hours and filtered on a celite bed, washing with THF. Evaporation is performed and the residue is extracted with DCM (15 mL), and the organic phase is washed with water (5 mL) and brine (5 mL), anhydriified and evaporated again.

For the derivatives in which the phenol oxhydryl is protected as TBD MS ether, the residue is dissolved in DCM (10 mL), and TB AF (6 mmol, 3 equiv.) is added. After 1 hour at room temperature, the mixture is diluted with DCM (5 mL), washed with water (3 x 5 mL) and brine (5 mL) and anhydriified (Na_2SO_4). After concentration, the residue is purified with flash chromatography on silica gel..

For the purification of these products chromatography on silica gel is used with an elution gradient of the following type: EtOAc:petroleum ether 1:9, 2:8, 3:7.

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-4-ol –

ST2151:

White solid, m.p. = 145-147°C; $^1\text{H-NMR}$ (CDCl_3) δ : 3.64 (s, 6H), 3.83 (s, 3H), 5.34 (s, 1H), 6.50 (d, $J=12.6$ Hz, 1H), 6.54 (s, 1H), 6.60 (d, $J=12.6$ Hz, 1H), 6.69 (s, 1H), 7.27 (s, 1H), 7.32 (d, $J=5.6$ Hz, 1H), 7.41 (d, $J=5.6$ Hz, 1H), 7.42 (s, 1H).

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thio-phen-4-ol –

ST2152:

Yellow solid, m.p. = 67-69°C; $^1\text{H-NMR}$ (CDCl_3) δ : 3.88 (s, 6H), 3.92 (s, 3H), 5.50 (s, 1H), 6.74 (s, 2H), 6.93 (s, 1H), 7.03 (s, 2H), 7.35 (d, $J=5.2$ Hz, 1H), 7.43 (d, $J=5.2$ Hz, 1H), 7.56 (s, 1H).

cis-4-Methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene –

ST2049:

Yellow oil. $^1\text{H-NMR}$ (CDCl_3) δ : 3.65 (s, 6H), 3.76 (s, 3H) 3.84 (s, 3H), 6.55 (s, 1H), 6.58 (d, $J=11.2$ Hz, 1H), 6.64 (d, $J=11.2$ Hz, 1H), 6.70 (s, 1H), 7.27 (s,

1H), 7.31 (d, J=5.0 Hz, 1H), 7.42 (d, J=5.0 Hz, 1H), 7.44 (s, 1H). FAB-MS (MALDI-TOF): 356.4 [M+1].

trans-4-Methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene – ST2050:

Yellow solid; m.p. = 171-173°C. ¹H-NMR (CDCl₃) δ: 3.89 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.78 (s, 2H), 6.95 (s, 1H), 7.10 (s, 2H), 7.33 (d, J=5.6 Hz, 1H), 7.47 (d, J=5.6 Hz, 1H), 7.58 (s, 1H). FAB-MS (MALDI-TOF): 356.3 [M+1].

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol – ST2179:

White solid that solidifies at +4°C; ¹H-NMR (CDCl₃) δ: 3.64 (s, 6H), 3.83 (s, 3H), 5.94 (s, 1H), 6.73 (s, 2H), 6.82 (d, J=6.0 Hz, 1H), 6.85 (d, J=2.2 Hz, 1H), 6.99 (s, 2H), 7.24 (d, J=6.0 Hz, 1H), 7.55 (d, J=2.2 Hz, 1H).

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol – ST2180:

Pale yellow solid, m.p. = 142-143°C; ¹H-NMR (CDCl₃) δ: 3.89 (s, 6H), 3.92 (s, 3H), 5.50 (s, 1H), 6.74 (s, 2H), 6.93 (s, 1H), 7.03 (s, 2H), 7.35 (d, J=5.2 Hz, 1H), 7.43 (d, J=5.2 Hz, 1H), 7.56 (s, 1H).

cis-4-Methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo-furan – ST2051:

Yellow oil. ¹H-NMR (CDCl₃) δ: 3.65 (s, 6H), 3.74 (s, 3H), 3.83 (s, 3H), 6.52 (s, 1H), 6.55 (d, J=11.2 Hz, 1H), 6.62 (d, J=11.2 Hz, 1H), 6.63 (s, 1H), 6.80 (s, 1H), 7.27 (s, 1H), 7.10 (s, 1H), 7.51 (s, 1H). FAB-MS (MALDI-TOF): 356.4 [M+1]. FAB-MS (MALDI-TOF): 340.6 [M+1].

trans-4-Methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran – ST2052:

Yellow solid, m.p. = 152-153°C; ¹H-NMR (CDCl₃) δ: 3.88 (s, 6H), 3.94 (s, 3H), 4.00 (s, 3H), 6.76 (s, 2H), 6.84 (s, 2H), 7.08 (s, 2H), 7.28 (d, J=2.2 Hz, 1H), 7.54 (d, J=2.2 Hz, 1H). FAB-MS (MALDI-TOF): 340.6 [M+1].

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-7-ol –

ST2487:

Brown solid, m.p. = 152-154°C; ¹H-NMR (CDCl₃) δ: 3.63 (s, 6H), 3.83 (s, 3H), 5.51 (s, 1H), 6.48 (d, J=12.2 Hz, 1H), 6.52 (s, 1H), 6.64 (d, J=12.2 Hz, 1H), 6.73 (s, 1H), 7.26 (s, 1H), 7.29 (d, J=3.2 Hz, 1H), 7.41 (d, J=3.2 Hz, 1H), 7.43 (s, 1H).

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thio-phen-7-ol –

ST2488:

Pale yellow solid, m.p. = 172-174°C; ¹H-NMR (CDCl₃) δ: 3.89 (s, 6H), 3.92 (s, 3H), 5.63 (s, 1H), 6.74 (s, 2H), 6.94 (s, 1H), 7.02 (d, J=2.8 Hz, 1H), 7.32 (d, J=5.2 Hz, 1H), 7.45 (d, J=5.2 Hz, 1H), 7.53 (s, 1H).

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol – ST2491

(27b):

White solid, m.p. = 140-141°C; ¹H-NMR (CDCl₃) δ: 3.63 (s, 6H), 3.83 (s, 3H), 5.33 (s, 1H), 6.46 (d, J=12.4 Hz, 1H), 6.52 (s, 1H), 6.57 (d, J=12.4 Hz, 1H), 6.69 (d, J=2.2 Hz, 1H), 6.82 (s, 1H), 7.12 (s, 1H), 7.26 (s, 1H), 7.58 (d, J=2.2 Hz, 1H).

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol – ST2492

(28b):

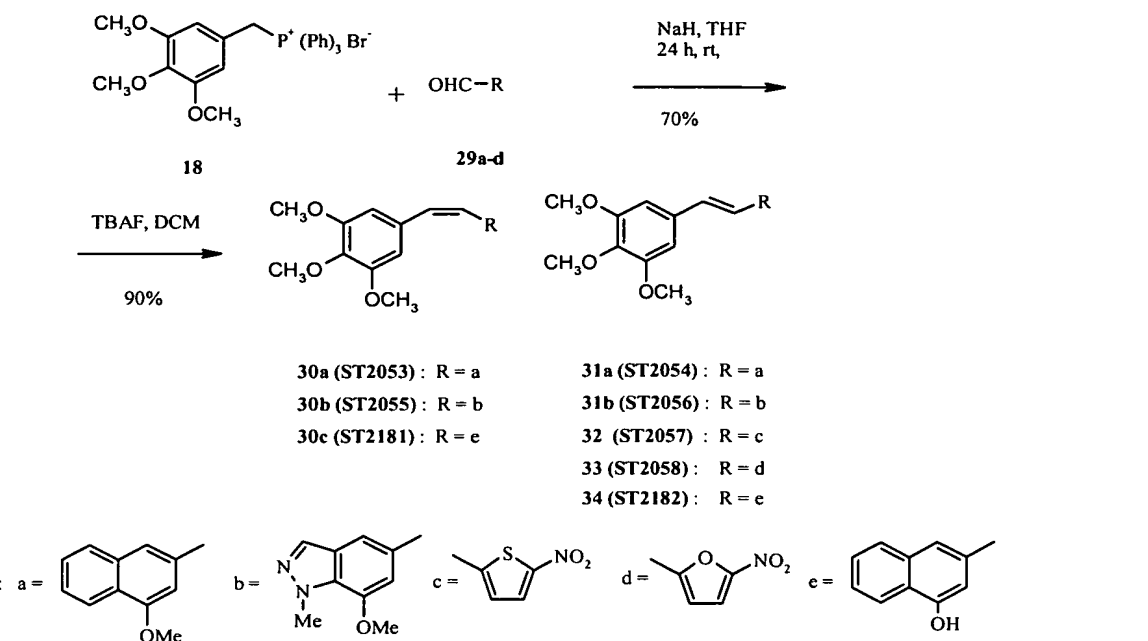
White solid, m.p. = 173-175°C; ¹H-NMR (CDCl₃) δ: 3.89 (s, 6H), 3.92 (s, 3H), 6.01 (s, 1H), 6.74 (s, 2H), 6.97 (s, 1H), 7.06 (d, J=3.2 Hz, 1H), 7.26 (d, J=5.2 Hz, 1H), 7.45 (d, J=5.2 Hz, 1H), 7.60 (s, 1H).

Example 4Preparation of ST2053, ST2054, ST2055, ST2056, ST2057, ST2058,
ST2181 and ST2182

These compounds are prepared according to synthesis diagram 6 here below:

Aldehydes 29a,b were prepared with a synthesis procedure in all respects similar to that used to prepare aldehydes 17a,d (Diagram 4).

SCHEMA 6



cis-1-Methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalene —

053:

Colourless oil. ¹H-NMR (CDCl₃) δ: 3.63 (s, 6H), 3.75 (s, 3H), 3.83 (s, 3H), 4.09 (s, 3H), 4.25 (s, 3H), 4.35 (s, 3H), 4.45 (s, 3H), 4.55 (s, 3H), 4.65 (s, 3H), 4.75 (s, 3H), 4.85 (s, 3H), 4.95 (s, 3H), 5.05 (s, 3H), 5.15 (s, 3H), 5.25 (s, 3H), 5.35 (s, 3H), 5.45 (s, 3H), 5.55 (s, 3H), 5.65 (s, 3H), 5.75 (s, 3H), 5.85 (s, 3H), 5.95 (s, 3H), 6.05 (s, 3H), 6.15 (s, 3H), 6.25 (s, 3H), 6.35 (s, 3H), 6.45 (s, 3H), 6.57 (s, 1H), 6.66 (d, J=13.2 Hz, 1H), 6.71 (d, J=13.2 Hz, 1H), 6.75 (s, 1H), 6.85 (s, 1H), 6.95 (s, 1H), 7.05 (s, 1H), 7.15 (s, 1H), 7.25 (s, 1H), 7.35 (s, 1H), 7.45 (s, 1H), 7.55 (s, 1H), 7.69 (m, 1H), 7.79 (m, 1H), 7.89 (m, 1H), 7.99 (m, 1H), 8.09 (m, 1H), 8.12 (m, 1H). FAB-MS (MALDI-TOF): 350.3 [M+1].

trans-1-Methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalene –

054:

Yellow solid; m.p. = 166-168°C. ¹H-NMR (CDCl₃) δ: 3.89 (s, 3H), 3.95 (s, 3H), 4.09 (s, 3H), 6.80 (s, 2H), 7.06 (s, 1H), 7.16 (s, 2H), 7.46 (m, 3H), 7.76 (dd, J=9.2 e 1.8 Hz, 1H), 8.20 (dd, J=9.2 e 1.8 Hz, 1H) . FAB-MS (MALDI-TOF): m/z 333 [M+1].

cis-7-Methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-

azole – ST2055:

White solid, m.p. 182-183°C; $^1\text{H-NMR}$ (CDCl_3) δ : 3.64 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 4.23 (s, 3H), 6.51 (d, $J=12.5$ Hz, 1H), 6.53 (s, 2H), 6.59 (d, $J=12.5$ Hz, 1H), 7.19 (s, 1H), 7.80 (s, 2H).

trans-7-Methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-indazole – ST2056:

Oil; $^1\text{H-NMR}$ (CDCl_3) δ : 3.86 (s, 3H), 3.91 (s, 6H), 4.01 (s, 3H), 4.28 (s, 3H), 6.73 (s, 2H), 6.94 (d, $J=15.8$ Hz, 1H), 7.06 (d, $J=15.8$ Hz, 1H), 7.31 (s, 1H), 7.86 (s, 2H).

2-Nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-thiophene – ST2057:

Yellowish oil, $^1\text{H NMR}$ (CDCl_3) δ 3.89 (s, 3H), 3.93 (s, 6H), 6.73 (s, 2H), 6.99 (d, 1H, $J = 4.4$ Hz), 7.06 (s, 2H), 7.85 (d, 1H, $J = 4.4$ Hz).

2-Nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-furan – ST2058:

Yellowish oil, $^1\text{H NMR}$ (CDCl_3) δ 3.90 (s, 3H), 3.92 (s, 6H), 6.53 (d, 1H, $J = 3.7$ Hz), 6.76 (s, 2H) 7.28 (s, 2H), 7.38 (d, 1H, $J = 3.6$ Hz).

cis-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol – ST2181:

Yellow solid, m.p. = 163-165°C; $^1\text{H-NMR}$ (CDCl_3) δ : 3.62 (s, 6H), 3.84 (s, 3H), 5.56 (s, 1H), 6.53 (d, $J=12.4$ Hz, 1H), 6.56 (s, 2H), 6.68 (d, $J=12.4$ Hz, 1H), 6.79 (s, 1H), 7.38 (s, 1H), 7.45 (m, 2H), 7.72 (dd, $J=9.8$ e 3.6 Hz, 1H), 8.11 (dd, $J=9.8$ e 3.6 Hz, 1H).

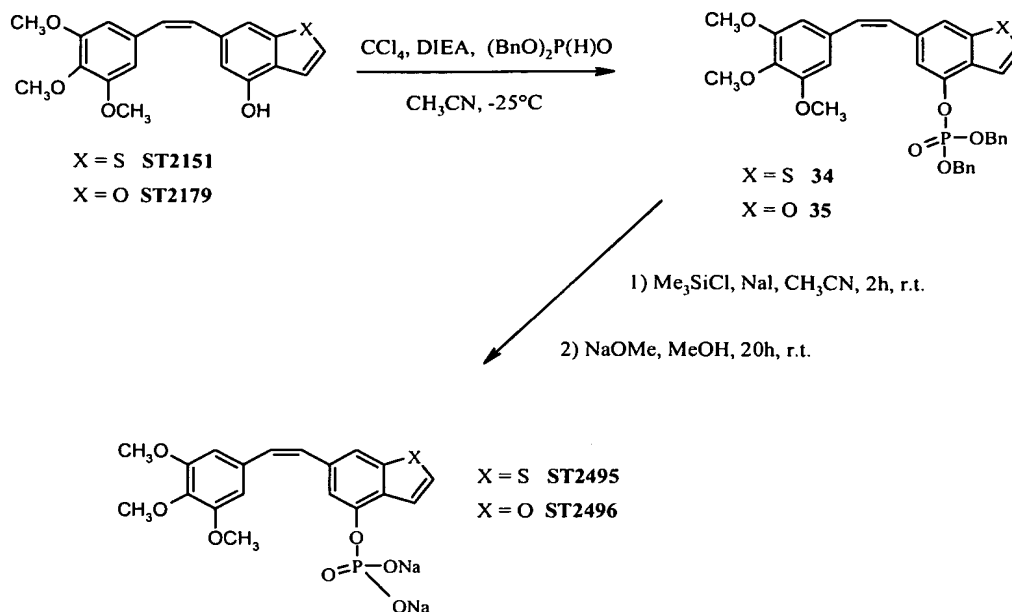
trans-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol – ST 2182:

Yellow solid, m.p. = 176-178°C; $^1\text{H-NMR}$ (CDCl_3) δ : 3.90 (s, 3H), 3.93 (s, 6H), 5.73 (s, 1H), 6.77 (s, 2H), 7.07 (m, 3H), 7.46 (m, 3H), 7.80 (dd, $J=9.6$ e 2.8 Hz, 1H), 8.14 (dd, $J=9.6$ e 2.8 Hz, 1H).

Example 5

Synthesis diagram 7

SCHEMA 7

General procedure for obtaining 34 and 35

To a solution of 1.2 mmol of ST2151 (or ST2179) in 5 mL of anhydrous CH_3CN , cooled to -25°C , were added 581 μL (6 mmol; 5 eq.) of CCl_4 . After approximately 10 minutes the following were added in the order indicated: 429 μL (2.59 mmol; 2.1 eq.) of diisopropylethylamine, 15 mg (0.12 mmol; 0.1 eq.) of dimethylaminopyridine and 383 μL (1.74 mmol; 1.45 eq.) of dibenzylphosphite. After 2 h at -10°C the reaction was complete and was added with 20 mL of KH_2PO_4 0.5 M, and the aqueous phase was shaken with AcOEt (3 x 10 mL). The organic phases were dried on anhydrous Na_2SO_4 and the crude product was purified by chromatography on SiO_2 with hexane: AcOEt 75:25 to give 1.05 mmol: yield: 88% of the expected product as a yellow oil.

6[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1-benzothiophen-4-yl 4-O-dibenzyl-phosphate (34). Fr = 0.11 in hexane/ AcOEt 8:2, MS- IS : $[\text{M}+\text{H}]^+ = 603.2$

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 3.6 (s, 6H, 2x OCH_3), 3.8 (s, 3H, OCH_3), 5.05 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.5 (s, 2H, 2x CH_{ar}), 6.6 (bs, 2H, 2x CH_{ar}), 7.2-7.4 (m, 11H, 11x CH_{ar}), 7.6 (s, 1H, CH_{ar}).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 56.1; 61.1; 70.3; 106.4; 115.9; 119.7; 120.4; 127.1; 128.2; 128.8; 128.9; 129.0; 131.1; 131.6; 132.2; 134.9; 135.6; 153.2.

6[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1-benzofuran-4-ol-4-O-dibenzyl-phosphate (35). Fr = 0.20 in hexane/AcOEt 7:3, MS- $\text{IS}:[\text{M}+\text{H}]^+ = 587.2$

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 3.6 (s, 6H, 2x OCH_3), 3.8 (s, 3H, OCH_3), 5.05 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.45 (s, 2H, 2x CH_{ar}), 6.55 (bs, 2H, 2x CH_{ar}), 6.75 (bs, 1H, CH_{ar}), 7.05 (s, 1H, CH_{ar}), 7.2-7.4 (m, 11H, 11x CH_{ar}), 7.5 (bs, 1H, CH_{ar}).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 56.1; 61.1; 70.3; 98.8; 104.3; 106.4; 109.1; 115.1; 119.9; 128.2; 128.8; 128.9; 129.2; 130.9; 132.3; 134.7; 135.5; 145.5; 153.2; 156.5.

General procedure for obtaining ST2495 and ST2496

To the solution of 1.2 mmol of dibenzyl-ester 34 (or 35) in 7 mL of anhydrous CH_3CN were added, at room temperature, 36 mg (2.4 mmol; 2 eq.) of NaI and then the solution of 303 μL (2.4 mmol; 2 eq.) of Me_3SiCl in 1 mL of anhydrous CH_3CN . After 2 h the reaction was complete and the minimum amount of water to solubilise the salts was added, as well as a 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution until decoloration of the reaction mixture was achieved. The solution thus obtained was shaken with AcOEt until complete extraction of the product in the organic phase; the organic phases were dried on Na_2SO_4 and the solvent removed in vacuo.

The crude oil thus obtained was dissolved in 4 mL of anhydrous MeOH, and 130 mg (2.4 mmol; 2 eq.) of NaOMe were added to the solution. The mixture was left at room temperature for 20 h, until complete salification was achieved. The solvent was then removed in vacuo and the residue washed with Et₂O to give 1.1 mmol (yield: 92%) of product as a white solid.

Disodium 6[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1-benzo-thiophen-4-ol 4-O-phosphate – ST2495.

T dec = 226°, MS-IS: [M-1]⁻ = 419.

¹H-NMR (300 MHz, D₂O) δ: 3.4 (s, 3H, OCH₃), 3.1 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 6.4-6.45 (d, 1H, CHolef), 6.5(s, 2H, 2xCHar), 6.1-6.15 (d, 1H, CHolef), 7.25-7.5 (m, 4H, 4xCHar).

¹³C-NMR (75 MHz, D₂O) δ: 30.4; 55.7; 56.0; 56.2; 61.1; 104.1; 106.9; 115.5; 116.6; 121.5; 121.6; 126.1; 126.3; 127.6; 128.3; 128.6; 128.9; 129.9; 130.7; 132.6; 132.7; 133.6; 134.3; 134.7; 136.1; 140.9; 141.6; 149.2; 152.3; 152.8.

Disodium 6[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1-benzo-furan-4-ol 4-O-phosphate – ST2496.

T dec = 212°, MS-IS: [M-1]⁻ = 403.

¹H-NMR (300MHz, D₂O) δ: 3.5 (s, 6H, 2xOCH₃), 3.6 (s, 3H, OCH₃), 6.4-6.45 (d, 1H, CHolef), 6.5(s, 2H, 2xCHar), 6.6-6.65 (d, 1H, CHolef), 6.85-7.1 (m, 3H, 3xCHar), 7.5 (s, 1H, CHar).

¹³C-NMR (75MHz, D₂O) δ: 30.4; 55.8; 56.0; 56.2; 61.1; 98.8; 104.1; 104.2; 104.8; 105.9; 106.8; 114.9; 120.3; 127.6; 128.0; 128.6; 129.7; 130.9; 133.7; 134.2; 136.1; 145.2; 147.4; 152.1; 152.3; 152.8; 156.0.

Also subjects of the present invention are the intermediate synthesis products 15a,b, 16a-d, 17a-d, 23a,b, 24a,b, and 26a,b described in diagrams 4 and 5.

Cell cultures and cytotoxicity tests

The cytotoxic effect of derivatives ST2151 and ST 2179 was evaluated in series of human and murine cell lines.

Human umbilical vein endothelial cells (HUVEC), from the BioWhittaker company, were maintained in EGM-2 culture medium (BioWhittaker).

Bovine microcirculatory endothelial cells (BMEC), isolated from bovine adrenal glands, were maintained in culture in DMEM containing 20% FBS, 50 µg/ml of bovine brain extract (BBE), 50 units/ml of heparin (SIGMA), 100 units/ml of gentami-cin (SIGMA) and 10 mg/ml of L-glutamine (Hyclone). EA-hy926, an immortalised hybridoma of HUVEC and adenocarcinoma cells, obtained from the University of Bari Department of Biomedical Sciences and Human Oncology, was cultured in DMEM added with 10% FBS and gentamicin.

The following cell lines, purchased from ATCC, were cultured according to the manufacturer's instructions: MeWo human melanoma, NCI-H460 human lung cancer, LoVo human colon adenocarcinoma, and PC3 human prostate carcinoma.

The M109 murine lung cancer line and the HT29 human colon adenocarcinoma line, obtained from the Milan Tumour Institute, were cultured in RPMI containing 10% FBS and antibiotics.

The B16/BL6 murine melanoma line, obtained from the M. Negri Institute in Milan, was cultured in DMEM containing 10% FBS and antibiotics.

For the cytotoxicity test the cells were seeded at variable densities according to cell type in 96-well plates in normal culture medium (200 µl/well) and incubated for 24 hours at 37°C. On the next day, the study substances were added at scalar concentrations and the cells were incubated for a further 24 hours at 37°C in a humidified atmosphere containing 5% CO₂. At the end of the incubation period the medium containing the substances was removed and three washings with PBS were performed. At the end of the washings 200 µl/well of fresh medium were added and the plates were incubated at 37°C for a further 48 hours. At the end of this incubation period the culture medium was removed by overturning the plates and 200 µl/well of PBS and 50 µl of 80% cold trichloroacetic acid (TCA) were added. The plates were then incubated in ice. After 1 h the TCA was removed, the plates were washed three times by immersion in distilled water and dried first on blotting paper and then in the oven. 200 µl of 0.4% sulforodamine B in 1% acetic acid were then added to all wells. The plates were incubated at room temperature for a further 30 minutes. The sulforodamine B was removed by overturning, the plates were washed three times by immersion in 1% acetic acid, and then dried first on blotting paper and then in the oven. 200 µl of Tris base 10 mM were then added to all wells and the plates were placed under stirring for at least 20 min. The optical density was measured by spectrophotometric readout at 540 nm.

Table 1 shows the IC₅₀ values of ST2151 and ST2179, that is to say the concentration capable of inhibiting cell survival by 50%, processed using ALLFIT software.

Table 1

Cell line	IC ₅₀ ± SE (nM)	
	ST2151	ST2179
BMEC	87±1	49±1
HUVEC	49±0.64	n.d.
EAHY.926	52±4.9	40±3.9
NCI-H460	74±2.9	53±1.3
M109	490±30	93±6
HT29	900±65	990±40
LoVo	360±0.01	490±0.04
PC3	120±0.01	100±0.01
B16/BL6	85±0.5	44±3.8
MeWo	68±5	71±17

Tubulin polymerisation inhibition test

The tubulin polymerisation test in the presence of ST2151 was performed as described by Shiff *et al.* (Biochemistry, 1981, 20: 3247-3252) with a number of modifications. In brief, tubulin rich in microtubule-associated proteins (MAP) was diluted to the concentration of 3 mg/ml in PEM buffer [100 mM PIPES (pH 6.9), 1 mM EGTA and 1 mM MgCl₂] containing 1 mM GTP (GPEM), and maintained in ice. The solution was placed at 37°C and polymerisation was monitored by measuring absorbance at 340 nm every 25 seconds with a spectrophotometer equipped with an electronic temperature control device (Cobas-Mira Analyzer). After 5 minutes, when the polymerised tubulin had reached a steady state, 5 µM Taxol, 1,35 µM Colcemid, or ST2151 were added and the absorbance measurements were taken for a further 15 min. The IC₅₀ values were determined by non-linear regression analysis using “Prism GraphPad” software.

The value indicated in Table 2 is the mean of 3 independent determinations.

Table 2

Compound	IC ₅₀ ± SE (μM)
ST2151	58.6 ± 2.7

Evaluation of anticancer activity

The anticancer activity of ST2151, ST2495 and ST2496 was assayed in an animal model of human lung carcinoma.

In this model, human NCI-H460 lung cancer cells at a density of 3 x 10⁶ cells/mouse were injected subcutaneously in the right flank of nude CD1 mice.

Starting from day 4 or day 6 after inoculation of the cancer, the animals were treated with the study molecules at various doses and according to various treatment schedules (see tables).

All the animals were weighed during the course of the treatment to adjust the drug administration volume and to record the percentage loss of body weight (%BWL).

Tumour growth was assessed by measuring the shorter diameter (width) and the longer diameter (length) of each tumour twice a week with a Vernier caliper, and the anticancer activity was evaluated in terms of percentage inhibition of tumour growth. The tumour volume was calculated using the following formula: tumour volume (TV) in mm³ = [length (mm) x width (mm)²]/2. The percentage inhibition (%TVI) was calculated according to the following equation: 100-[(mean tumour volume of the treated group / mean tumour volume of the control group) x 100]. A value of $P \leq 0.05$ was regarded as statistically significant.

The results of the experimentation with ST2151 and ST2495 and with ST2496 are presented in Tables 3 and 4, respectively.

Table 3

Treatment	n	% BWL	Mortality	%TVI Days after tumour inoculation	
				10	13
Vehicle (10% DMSO)	7	0	0/7	/	/
ST2151 i.p. 25 mg/kg	7	0	0/7	95**	87**
Vehicle (saline)	7	0	0/7	/	/
ST2495 p.o. 25 mg/kg	7	0	0/7	68*	64*
ST2495 i.p. 25 mg/kg	7	0	0/7	85**	72**

The compounds were administered orally (p.o.) or intraperitoneally (i.p) at the dose of 25 mg/kg on days 6 and 10 after inoculation of the tumour.

* $P < 0.05$; ** $P < 0.01$

Table 4

Treatment	N	% BW	Mortality	%TVI Days after tumour inoculation			
				4	7	11	14
Vehicle (saline)	8	0	0/8	/	/	/	/
ST2496 p.o. 30 mg/kg	8	0	0/8	0	31	45**	57**

The compound was administered orally (p.o.) at the doses indicated from day 4 to day 14 after inoculation of the tumour according to the qdx5/w schedule.

* $P < 0.05$; ** $P < 0.01$

As can be seen from the tables, intraperitoneal administration of ST2151 proved significantly active in inhibiting tumour volume, whereas ST2495 proved active both orally and intraperitoneally.

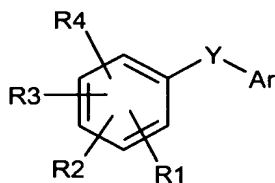
ST2496, too, when administered orally, brought about a significant inhibition of the tumours as compared to controls.

In keeping with another subject of the present invention, the pharmaceutical compositions contain at least one formula (I) compound as the active ingredient, in an amount such as to produce a significant therapeutic effect. The compositions covered by the present invention are entirely conventional and are obtained using methods which are common practice in the pharmaceutical industry, such as are illustrated, for example, in *Remington's Pharmaceutical Science Handbook*, Mack Pub. N.Y. – latest edition. According to the administration route opted for, the compositions will be in solid or liquid form, suitable for oral, parenteral or intravenous administration. The compositions according to the present invention contain at least one pharmaceutically acceptable vehicle or excipient along with the active ingredient. They may be particularly useful coadjuvant agents in

formulation, e.g. solubilising agents, dispersing agents, suspension agents and emulsifying agents.

CLAIMS

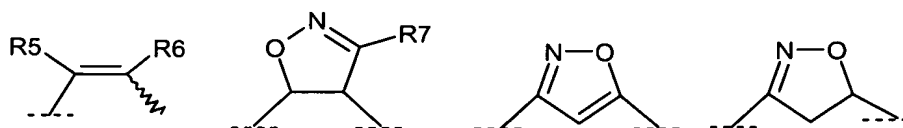
1. Formula (I) compounds



in which:

the various R_1 , R_2 , R_3 and R_4 , which can be the same or different, are H, OH, OPO_3Na_2 , OMe, NO_2 , F, Cl, Br;

Y is a group selected from:

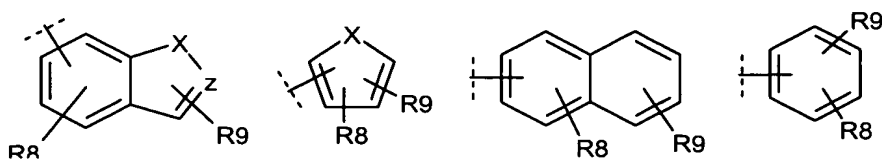


~~~~~ : *cis o trans*

$R_5$  and  $R_6$ , which can be the same or different, are H, or halogen, but cannot both be simultaneously H;

$R_7$  is H, OMe,  $SO_2Ph$ ;

Ar is a group selected from:



$R_8$  and  $R_9$ , which can be the same or different, are H, OH, OMe,  $OPO_3Na_2$ ,  $NH_2$ ,  $NHR_{10}$ ,  $NO_2$ , or halogen;

$R_{10}$  is  $C_1$ - $C_4$  alkyl or acyl;

X is O, S, N,  $NR_{11}$ ;

$R_{11}$  is H,  $CH_3$ ,  $CH_2Ph$ ;

Z is CH, N;

their enantiomers, diastereoisomers, the respective mixtures and their pharmaceutically acceptable salts.

2. Compound according to claim 1, selected from the group consisting of:

2-methoxy-5-[3-methoxy-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-phenol;

2-methoxy-5-[3-methoxy-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol;

5-[3-benzenesulphonyl-4-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-4-isoxazolyl]-2-methoxy-phenol;

5-[3-benzenesulphonyl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-2-methoxy-phenol;

2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-5-isoxazolyl]-phenol;

2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-3-isoxazolyl]-phenol;

2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-3-isoxazole]-phenol;

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-4-ol;

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thio-phen-4-ol;

cis-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene;



trans-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene;

cis-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol;

trans-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-4-ol;

cis-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran;

trans-4-methoxy-6-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran;

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-7-ol;

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophen-7-ol;

cis-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol;

trans-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran-7-ol;

cis-1-methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalene;

methoxy-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalene;

cis-7-methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-indazole;

trans-7-methoxy-1-methyl-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-indazole;

2-nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-thiophene;

2-nitro-5-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-furan;

cis-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol;

trans-3-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-naphthalen-1-ol;

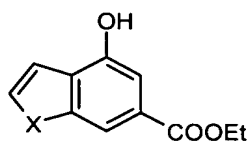
disodium 6[(Z)-2-(3,4,5-trimethoxy-phenyl)ethenyl]-1-benzo-thiophen-4-ol 4-O-phosphate;

disodium 6[(Z)-2-(3,4,5-trimethoxy-phenyl)ethenyl]-1-benzo-furan-4-ol 4-O-phosphate.

3. Use of compounds according to claims 1-2 as medicines.

4. Use of compounds according to claims 1-2 for the preparation of a medicine for the treatment of oncological-type diseases.
5. Use of compounds according to claims 1-2 for the preparation of a medicine for the treatment of cancers that respond to cytotoxic activity.
6. Use according to claim 5, in which said cancer is selected from the group consisting of sarcoma, carcinoma, carcinoid, bone cancer, neuroendocrine cancer, lymphoid leukaemia, myeloid leukaemia, monocytic leukaemia, megakaryocytic leukaemia, or Hodgkin's disease.
7. Use of compounds according to claim 1 for the preparation of a medicine for the treatment of diseases related to abnormal angiogenesis..
8. Use according to claim 7, in which said disease is selected from the group consisting of arthritic disease, tumours responding to antiangiogenic activity, metastatic spread, diabetic retinopathy, psoriasis, chronic inflammation, and atherosclerosis.
9. Use according to any one of claims 4 to 8, in which, in the treatment of tumours, the compounds according to claims 1-2 are combined with at least one other antitumour drug.
10. Use according to claim 9, in which said antitumour drug is selected from the group consisting of alkylating agents; topoisomerase inhibitors; antitubulin agents; intercalating agents; antimetabolites; naturally occurring products such as Vinca alkaloids, epipodophyllotoxins, antibiotics, enzymes, taxanes and anticancer vaccines.
11. Pharmaceutical composition containing as the active ingredient a compound according to claims 1-2 in a mixture with a pharmaceutically acceptable excipient or diluent.

12. Use of the compound with the formula

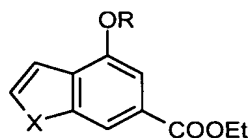


in which

X is oxygen or sulphur, as an intermediate product for the preparation of compounds according to claims 1-2.

13. Compound with the formula

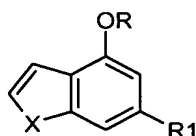
:



in which

X is oxygen or sulphur, R is methyl, or terbutyl-dimethylsilyl.

14. Compound with the formula

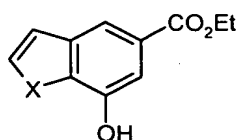


in which

X is oxygen or sulphur, R is methyl, or terbutyl-dimethylsilyl.

R<sub>1</sub> is formyl.

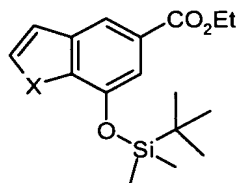
15. Use of the compound with the formula



in which

X is oxygen or sulphur, as an intermediate product for the preparation of compounds according to claims 1-2.

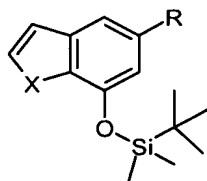
16. Compound with the formula



in which

X is oxygen or sulphur.

17. Compound with the formula



in which

X is oxygen or sulphur.

18. Use of compounds according to claims 13-14 and 16-17 as intermediate products in the preparation of compounds according to claims 1-2.

on behalf of SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.